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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,903	01/20/2006	David W. Morris	PP23369.0003/20366-034US1	3389

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,903	MORRIS ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32,38,40-45,48,52,54,55,58,79-81,83-91 and 93-98* is/are pending in the application.

4a) Of the above claim(s) *32,38,40-45,48,54,55,58 and 95-98* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52,79-81,83-91,93 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed May 7, 2010. Claims 32, 38, 40-45, 48, 52, 54, 55, 58 and 79-95 were previously pending, with claims 32, 38, 40-45, 48, 54, 55, 58 and 95-98 withdrawn from further consideration. Applicants cancelled claims 82 and 92 and amended claims 52, 79, 83, 84, 90 and 91. Claims 52, 79-81, 83-91, 93 and 94 will be examined.

2. Applicants' claim cancellations obviated all of the previously presented rejections for claims 82 and 92. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" section below.

3. Applicants' amendments to the specification obviated the previously presented objections.

Response to Arguments

4. Applicant's arguments filed May 7, 2010 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 52, 79-81, 83-91, 93 and 94 under 35 U.S.C. 112, first paragraph, written description, Applicants argue that

"The Applicants assert that the specification discloses that nucleic acids can have variants and how to determine the identity between the variants in paragraphs [0062]-[0071]. The Applicants have also disclosed the claimed nucleic acid sequence (SEQ ID NO:41). Based on this disclosure and the claims as currently amended, the Applicants submit that one of skill in the art would find that the Applicants were in possession of the claimed invention."

However, the issue here is not the disclosure that any sequence can have variants and how to determine their existence, but whether Applicants were in possession of any variants of SEQ ID NO: 41. The answer is clearly no, since not a single variant of SEQ ID NO: 41 was disclosed.

The rejection is maintained.

B) Regarding the rejection of claims 52, 79-81, 83-91, 93 and 94 under 35 U.S.C. 112, first paragraph, written description, Applicants argue that

"The Applicants claims are directed to methods of diagnosing kidney cancer by examining a specific gene. The specification discloses several methodologies with which to determine differential expression, for example, paragraphs [0159]-[0166] and Examples 2, 3, 5 and 9. Given the disclosure in the specification and the claims as currently amended, the Applicants submit that one of skill in the art could make and use the claimed invention without undue experimentation."

Again, the issue is not the fact that Applicants did not disclose methods of determining differential expression of genes, which were known in the art at the time of the invention. Applicants did not provide evidence that any sequence either 95% or 98% identical to SEQ ID NO: 41 is differentially expressed in any kidney cancer. Further, even association of SEQ ID NO: 41 with renal carcinoma is not convincing, since it was upregulated in only one out of twelve renal carcinomas, and no data was presented of how the upregulation was detected. Therefore, in order for one of ordinary skill in the art to practice the invention as claimed, screening of different types of kidney cancers would need to be performed for differential expression of SEQ ID NO: 41 or sequences 95 or 98% identical to it. Finally, as can be seen from PubMed search with terms "TP53I11 and (cancer* or tumor* or carcinoma*)" up to date only two papers published in 2009, suggest involvement of a nucleic acid with SEQ ID NO: 41 in hepatocellular carcinogenesis. No references were found suggesting its involvement in kidney cancers. Therefore, the claims are not enabled even seven years after the filing date of the earliest application.

The rejection is maintained.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 52, 79-81, 83-91, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

All of the current claims encompass a genus of nucleic acids which are different from those disclosed in the specification. The genus includes variants for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named SEQ ID NO: 41. Specifically, Applicants claim a method of diagnosing kidney cancer by detecting a level of expression of a nucleic acid with 95% or 98% sequence identity to SEQ ID NO: 41 or complements thereof. First, Applicants showed that SEQ ID NO: 41 is overexpressed in 1 out of 12 renal cell carcinomas, which is not an indication that SEQ ID NO: 41

has diagnostic potential in kidney cancer. Then, Applicants did not show that any other nucleic acids related to SEQ ID NO: 41, such as sequences having 95 or 98% identity to SEQ ID NO: 41 were upregulated in any kidney cancers. The genus of sequences with 95% sequence identity to SEQ ID NO: 41 (4099 bp) has $4^{205} = 9.6 \times 10^{123}$ members, and the genus of sequences 98% identical to SEQ ID NO: 41 has $4^{82} = 1.2 \times 10^{49}$ members.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

> "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the sequences 95% or 98% identical to SEQ ID NO: 41 lack any specific structure, is precisely the situation of naming a type of material which is generally known to likely exist, but, except for one specific sequence, is in the absence of knowledge of the material composition and fails to provide descriptive support for the generic claim to "a method of diagnosing kidney cancer comprising: comparing a level of nucleic acid comprising a nucleotide sequence at least 95% identical to SEQ ID NO: 41 in a patient sample…", for example.

In the instant application, certain specific SEQ ID NOs are described. Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

> "...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any nucleic acids other than those expressly disclosed which is SEQ ID NO: 41. Therefore, the claims fail to meet the written description requirement by encompassing sequences which are not described in the specification.

7. Claims 52, 79-81, 83-91, 93 and 94 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 52, 79-81, 83-91, 93 and 94 are broadly drawn to a method for diagnosing kidney cancer comprising:

comparing a level of nucleic acid comprising a human nucleotide sequence at least 95% identical to SEQ ID NO: 41 in a patient sample comprising human kidney tissue to a level of nucleic acid in a control sample, wherein an increase of at least 50% from the level of nucleic acid

in the patient sample compared to the level of the nucleic acid in the control sample indicates that the patient has kidney cancer.

However, as will be further discussed, there is no support in the specification for the claimed method. The invention is a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Working Examples

The specification has no working examples of diagnosing kidney cancer using a level of expression of SEQ ID NO: 41 or sequences with 95% or 98% sequence identities to SEQ ID NO: 41. The only data presented in Table 14 indicates that SEQ ID NO: 41 is upregulated in one out of twelve kidney carcinomas.

Guidance in the Specification.

The specification provides no evidence that the disclosed nucleic acid sequence with SEQ ID NO: 41 would have usefulness in diagnosing cancer. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses that the polynucleotide with SEQ ID NO: 41 was upregulated in one of twelve renal cell carcinomas (see page 87, Table 14). Therefore, there is no evidence that SEQ ID NO: 41 has diagnostic value even for kidney carcinomas. Further, Applicants claim that SEQ ID NO: 41 encodes a polypeptide with signaling activity. No evidence of such activity was provided at the time of invention.

The unpredictability of the art and the state of the prior art

The specification shows that SEQ ID NO: 41 was upregulated in one of twelve renal cell carcinomas (page 87, Table 14). The specification does not provide information on how it was

determined that the gene was upregulated. In case it was done by microarray hybridization, the results may not be reliable, as evidenced by the references discussed here. Li et al. (J. Theor. Biol., vol. 219, pp. 539-551, 2002; cited in the previous office action) disclosed that selection of overexpressed genes by either "fold change" or t-test is not reliable method, as the selection of threshold is arbitrary (page 539, last paragraph; page 540, paragraphs one and two). Wang et al. (Bioinformatics, vol. 20, pp. 100-104, 2004; cited in the previous office action) again stresses that either the fold method or t-test method for picking differentially expressed genes are not reliable, since the fold method does not take variations within treatments into consideration, and the optimal performance of the t-test depends on sample size and assumption that expression intensities have normal distribution (page 100, third and fourth paragraphs). Finally, as pointed out by Dumur et al. (Clin. Chem., vol. 50, pp. 1994-2002, 2004; cited in the previous office action), the quality of RNA or cDNA used in the microarray hybridization affects the outcome of the experiments (page 1995, second paragraph).

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to be able to find out whether SEQ ID NO: 41 or sequences related to it have diagnostic value in any type of kidney cancer, including determining expression levels of SEQ ID NO: 41 or sequences related to it in a large number of kidney cancers. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the determination of gene upregulation depends on the multitude of factors and the method used, the factor of unpredictability weighs heavily in favor of undue experimentation. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

8. No references were found teaching or suggesting claims 52, 79-81, 83-91, 93 and 94, but they are rejected for reasons given above.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
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/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
June 30, 2010